In the Specification

Please replace the paragraph beginning on page 19, line 14 with the following amended paragraph:

Based on these data and excluding the six cysteines, we judge that the KuDom structure will allow those substitutions shown in Table 9. The class indicates whether the substitutions: A) are very likely to give a stable protein having substantially the same binding to hNE, hCG, or some other serine protease as the parental sequence, B) are likely to give similar binding as the parent, or C) are likely to give a ~~proteins~~protein retaining the KuDom structure, but which are likely to affect the binding. Mutants in class C must be tested for affinity, which is relatively easy using a display-phage system, such as the one set forth in W0/02809. The affinity of hNE and hCG inhibitors is most sensitive to substitutions at positions 15, 16, 17, 18, 34, 39, 19, 13, 11, 20, 36 of BPTI, if the inhibitor is a mutant of ITI-D1, these positions must be converted to their ITI-D1 equivalents by aligning the cysteines in BPTI and ITI-D1.

Please replace the paragraph beginning on page 35, line 2 with the following amended paragraph:

Example 9: Amino-acid sequences of EPI-HNE-3 and EPI-HNE-4

Table 10 gives amino acid sequences of four human-neutrophil-elastase (hNE) inhibitor proteins: EPI-HNE-1 (which is identical to EpiNE1), EPI-HNE-2, EPI-HNE-3, and EPI-HNE-4. These proteins have been derived from the parental Kunitz-type domains shown. Each of the proteins is shown aligned to the parental domain using the six cysteine residues (shaded) characteristic of the Kunitz-type domain. Residues within the inhibitor proteins that differ from those in the parental protein are in upper case. Entire proteins having the sequences EPI-HNE-1, EPI-HNE-2, EPI-HNE-3, and EPI-HNE-4 (Table 10) have been produced. Larger proteins that comprise one of the hNE-inhibiting sequences are expected to have potent hNE-inhibitory activity; EPI-HNE-1, EPI-HNE-2, EPI-HNE-3, and EPI-HNE-4 are particularly preferred. It is expected that proteins that comprise a significant part of one of the hNE-inhibiting sequences found in Table 10 (particularly if the sequence starting at or before the first cysteine and continuing through or beyond the last cysteine is retained) will exhibit potent hNE-inhibitory activity.

Please replace the paragraph beginning on page 36, line 11 with the following amended paragraph:

We have used this high density *Pichia pastoris* production system to produce proteins by secretion into the cell ~~CM~~culture medium. Expression plasmids were constructed by ligating synthetic DNA sequences encoding the *S. cerevisiae* mating factor α prepro peptide fused directly to the amino terminus of the desired hNE inhibitor into the plasmid pHIL-D2 using the *Bst*BI and the *Eco*RI sites shown. Table 24 gives the DNA sequence of a *Bst*BI-to-*Eco*RI insert that converts pHIL-D2 into pHIL-D2(MFα-PrePro::EPI-HNE-3). In this construction, the fusion protein is placed under control of the upstream inducible *P. pastoris aox1* gene promoter and the downstream *aox1* gene transcription termination and polyadenylation sequences. Expression plasmids were linearized by *Sac*I digestion and the linear DNA was incorporated by homologous recombination into the genome of the *P. pastoris* strain GS115 by spheroplast transformation. Regenerated spheroplasts were selected for growth in the absence of added histidine, replated, and individual isolates were screened for methanol utilization phenotype (*mut*$^+$), secretion levels, and gene dose (estimated via Southern hybridization experiments). High level secretion stains were selected for production of hNE inhibitors: PEY-33 for production of EPI-HNE-2 and PEY-43 for production of EPI-HNE-3. In both of these strains, we estimate that four copies of the expression plasmid are integrated as a tandem array into the *aox1* gene locus.

Please replace Table 21, page 89 with the following amended Table:

TABLE 21

ITI-D1-derived hNE Inhibitors

WEAK (K_D > 10^{-8} **M**)

```
                1    1     2   2    3    3    4    4    5    5
    1...5....0....5.....0...5....0....5....0....5....0....5...
1.  KEDSCQLGYSAGPCMGMTSRYFYNGTSMACETFQYGGCMGNGNNFVTEKDCLQTCRGA
```

MODERATE (10^{-8} > RD 22 10^{-9})

```
2.  KEDSCQLGYSAGPCVAMFPRYFYNGTSMACETFQYGGCMGNGNNFVTEKDCLQTCRGA
3.  RPDFCQLGYSAGPCMGMTSRYFYNGTSMACETFQYGGCMGNGNNFVTEKDCLQTCRGA
```

STRONG (10^{-9} > KD > 10^{-11} D)

```
4.  RPDFCQLGYSAGPCVAMFPRYFYNGTSMACETFQYGGCMGNGNNFVTEKDCLQTCRGA
5.  RPDFCQLGYSTGPCVAMFPRYFYNGTSMACETFQYGGCMGNGNNFVTEKDCLQTCRGA
6.  KEDFCQLGYSAGPCVAMFPRYFYNGTSMACETFQYGGCMGNGNNFVTEKDCLQTCRGA
7.  KPDSCQLGYSAGPCVAMFPRYFYNGTSMACETFQYGGCMGNGNNFVTEKDCLQTCRGA
8.  RPDFCQLGYSAGPCIGMFSRYFYNGTSMACETFQYGGCMGNGNNFVTEKDCLQTCRGA
```

VERY STRONG (K_D < 10^{-11} **M**)

```
9.  RPDFCQLGYSAGPCVAMFPRYFYNGTSMACQTFVYGGCMGNGNNFVTEKDCLQTCRGA
10. RPDFCQLGYSAGPCVAMFPRYFYNGASMACQTFVYGGCMGNGNNFVTEKDCLQTCRGA
11. RPDFCQLGYSAGPCVAMFPRYFYNGTSMACETFVYGGCMGNGNNFVTEKDCLQTCRGA
12. RPDFCQLGYSAGPCVGMFSRYFYNGTSMACQTFVYGGCMGNGNNFVTEKDCLQTCRGA
```

Residues shown underlined and bold are changed from those present in ITID1

Sequences Key:

1. ITI-D1 SEQ ID NO. ~~008~~16
2. ITI-D1E7 SEQ ID NO. ~~009~~21
3. BITI SEQ ID NO. ~~030~~141
4. BITI-E7 SEQ ID NO. ~~010~~142
5. BITI-E7-1222 SEQ ID NO. ~~012~~143
6. AMINO1 SEQ ID NO. ~~015~~22
7. AMINO2 SEQ ID NO. ~~016~~23
8. MUTP1 SEQ ID NO. ~~014~~24
9. BITI-E7-141 SEQ ID NO. ~~011~~17
10. MUTT26A SEQ ID NO. 018
11 MUTQE SEQ ID NO. 017
12 MUT1619 SEQ ID NO. ~~013~~20

Please replace Table 65, beginning on page 72 to page 73, with the following amended Table:

Table ~~65~~9: Definition of Class A, B and C mutations in PCT/US92/01501.

Classes:	A	No major effect expected if molecular charge stays in range -1 to +1.
	B	Major effects not expected, but are more likely than in "A".
	C	Residue in the binding interface; any change must be tested.
	X	No substitution allowed.

Res. Id.	EpiNE1 (SEQ ID NO:7)	Substitutions	Class
1	R	any	A
2	P	any	A
3	D	any	A
4	F	Y, W, L	B
5	C	C	X
6	L	non-proline	A
7	E	L, S, T, D, N, K, R	A
8	P	any	A
9	P	any	A
10	Y	non-proline prefr'd	B
11	T	any	C
12	G	must be G	X
13	P	any	C
14	C	C strongly preferred, any non-proline	C
15	I	V, A	C
16	A		C
17	F	L, I, M, Y, W, H, V	C
18	F	Y, W, H	C
19	P	any	C
20	R	non-proline prefr'd	C
21	Y	F & Y most prefr'd; W, I, L prefr'd; M, V allowed	C
22	F	Y & F most prefr'd; non-proline prefr'd	Y, F B
23	Y	Y & F strongly prefr'd	F ,Y B
24	N	non-proline prefr'd	A
25	A	any	A

26	K	any	A
27	A	any	A
28	G	non-proline prefr'd	A
29	L	non-proline prefr'd	A
30	C	must be C	X
31	Q	non-proline prefr'd	B
32	T	non-proline prefr'd	B
33	F	F very strongly prefr'd; Y possible	X
34	V	any	C
35	Y	Y most prefr'd; W prefr'd; F allowed	B

Res. Id.	EpiNE1	Substitutions	Class
36	G	G strongly prefr'd; S, A prefr'd;	C
37	G	must be G so long as 38 is C	X
38	C	C strongly prefr'd	X
39	M	any	C
40	G	A,S,N,D,T,P	C
41	N	K,Q,S,D,R,T,A,E	C
42	G	any	C
43	N	must be N	X
44	N	S,K,R,T,Q,D,E	B
45	F	Y	B
46	K	any non-proline	B
47	S	T, N, A, G	B
48	A	any	B
49	E	any	A
50	D	any	A
51	C	must be C	X
52	M	any	A
53	R	any	A
54	T	any	A
55	C	must be C	X
56	G	any	A
57	G	any	A
58	A	any	A

prefr'd stands for preferred.

Please replace Table 11, beginning on page 80 to page 81, with the following amended Table:

Table 11: Restriction sites in plasmid pHIL-D2

pHIL-D2, 93-01-02 Ngene = 8157

Non-cutters

AflII	ApaI	AscI	AvaI	AvrII	BamHI	BglII
Bsp120I	BsrGI	BssHII	BstEII	FseI	MluI	NruI
PacI	PmlI	RsrII	SacII	SexAI	SfiI	SgfI
SnaBI	SpeI	Sse8387I	XhoI(PaeR7I)		XmaI(SmaI)	

Cutters

AatII GACGTc	1	5498	
AflIII Acrygt	1	7746	
AgeI Accggt	1	1009	
BlpI GCtnagc	1	597	
BspEI(BspMII,AccIII) Tccgga	1	3551	
BspMI gcaggt	1	4140	
Bst1107I GTAtac	1	7975	
BstBI(AsuII) TTcgaa	2	945	4780
Bsu36I CCtnagg	1	1796	
Ecl136I GAGctc	1	216	
EcoRI Gaattc	1	956	
EspI(Bpu1102I) GCtnagc	1	597	
HpaI GTTaac	1	1845	
NcoI Ccatgg	1	3339	
NdeI CAtatg	1	7924	
NsiI(Ppu10I) ATGCAt	1	684	
PflMI CCANNNNntgg	1	196	(SEQ ID NO:127)

PmeI	GTTTaaac	1	420
PstI	CTGCAg	1	6175
PvuI	CGATcg	1	6049
SapI	gaagagc	1	7863
SacI	GAGCTc	1	216
SalI	Gtcgac	1	2885
ScaI	AGTact	1	5938
SphI	GCATGc	1	4436
StuI	AGGcct	1	2968
SwaI	ATTTaaat	1	6532
Tth111I	GACNnngtc	1	7999
XbaI	Tctaga	1	1741
XcmI	CCANNNNNnnnntgg	1	711 (SEQ ID NO:128)

Aox1 5'	1 to about 950
Aox1 3'	950 to about 1250
His4	1700 to about 4200
Aox1 3'	4500 to 5400
bla	5600 to 6400
f1 ori	6500 to 6900

Please replace Table 630 on page 123 with the following amended Table:

Table ~~630~~40: Temperature stability of EPI-HNE proteins

Temperature (°C)	Residual hNE Inhibitory Activity			
	EPI-HNE-1	EPI-HNE-2	EPI-HNE-3	EPI-HNE-4
0	97	101	96	100
23	100	103	105	103
37	100	97	99	98
45	103			
52		101	100	
55	99			98
65	94	95	87	
69				82
75	100			
80		101	79	
85	106			63
93		88	57	
95	64			48

Proteins were incubated at the stated temperature for 18 hours in buffer at pH 7.0. In all cases protein concentrations were 1 μM. At the end of the incubation period, aliquots of the reactions were diluted and residual hNE-inhibition activity determined.